EXHIBIT 8

ORIGINAL ARTICLE

Evaluation of the tamper-resistant properties of tapentadol extended-release tablets: Results of in vitro laboratory analyses

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ABSTRACT

Objective: *To evaluate tamper-resistant properties of tapentadol tablets formulated with polyethylene oxide (PEO) matrix.*

Design: *Analytical and physical tests to characterize tablets.*

Interventions: *Tapentadol extended release (ER) 50, 100, 150, 200, and 250 mg.*

Main outcome measure(s): *Mechanical resistance of tapentadol ER tablets to crushing (all doses), in vitro drug-release profiles of intact and tampered 50- and 250-mg tablets, and resistance to extraction of 250-mg tablets subjected to hammering.*

Results: *Crush resistance testing showed no deformation of tablets with two metal spoons, minimal deformation (no pulverization/breakage) with a pill crusher, slight deformation with a standardized pharmacopeia breaking force tester, and flattening (no pulverization/breakage) with a standardized hammer instrument. Mean in vitro release profiles in quality control medium (0.050 M phosphate buffer, pH 6.8) were similar with intact and tampered (pill crusher) tablets; the release profile was faster for hammered than intact tablets, with 30 percent of the drug released after 30 minutes (slightly higher than maximum release allowed per drug product specifications). Intact tablets were completely resistant to extraction in most organic solvents tested; in aqueous solvents, the amount of drug extracted increased with time. Hammered tablets were less resistant to extraction but required vigorous shaking over extended periods of time to release >50 percent of active ingredient.*

Conclusions: *In vitro results from tampering attempts presented herein demonstrate that tapentadol ER tablets were resistant to these forms of physical manipulation. Tapentadol ER tablets were also generally resistant to dissolution in most solvents. Developing tamper-resistant formulations is an important step in strategies to mitigate opioid abuse.*

INTRODUCTION

The prescription of opioid analgesics has increased dramatically over the past 10-15 years worldwide[1-3]; this increase in the number of opioid prescriptions is largely related to efforts to address inadequately managed chronic pain.[4] In the United States, the increased availability of opioids has been accompanied by a corresponding increase in the rates of opioid abuse and diversion.[4,5] Achieving a balance between reducing the risks associated with opioid analgesics and allowing patients with pain to have necessary access to opioid therapy is the fundamental goal of opioid risk management.[4] Extended-release formulations of oral opioid analgesics provide sustained pain relief with less frequent dosing than immediate-release formulations, which is advantageous for managing chronic pain

and may result in improved patient adherence to treatment.[6] However, extended-release opioid analgesics may be more attractive for abuse or misuse because they contain higher doses of active ingredients than corresponding immediate-release formulations.[7] As such, the ease with which the extended-release formulation of an opioid analgesic can be manipulated to provide access to the active ingredients may make an extended-release analgesic more appealing to potential abusers.[8]

Several government agencies have addressed the need to deter abuse of oral opioid analgesics. Recent draft guidance from the US Food and Drug Administration (FDA) stated that abuse-deterrent opioid formulations should challenge methods by which opioids are known to be or expected to be abused.[9] To this end, a bill called the "Stop Tampering of Prescription Pills (STOPP) Act of 2013" was proposed in the US House of Representatives and referred to the Committee on Energy and Commerce for evaluation.[10] Under this legislation (H.R. 486), manufacturers' new drug applications (NDAs) or abbreviated NDAs (ANDAs) for oral opioids would be required to demonstrate that the formulation possesses safety properties that deter abuse. This requirement would be enforceable for new brand or generic agents containing the same active ingredient as an already-approved tamper-resistant drug.[10] At the time of writing, this bill has not yet been enacted. The Centers for Disease Control and Prevention (CDC) also are promoting methods for curbing prescription drug abuse. In a February 2013 press release, the CDC mentioned "promising" steps taken by federal and state governments to prevent overdoses, including "encouraging the development of abuse-deterrent opioid formulations."[11] Further, in recent testimony before the US Senate Subcommittee on Crime and Drugs, Dr. Leonard Paulozzi, a CDC epidemiologist, stated that "... drug manufacturers should modify opioid painkillers so that they are more difficult to tamper with and/or combine them with agents that block the effect of the opioid if it is dissolved and injected."[12]

Tapentadol is a centrally acting analgesic with both μ-opioid receptor agonist and norepinephrine reuptake inhibitor activities.[13] In contrast to classical opioids, tapentadol immediate release (IR; NUCYNTA®, Janssen Pharmaceuticals, Inc.), which has been available in the United States since June 2009, is associated with an inherently low abuse liability.[14] In a study using data gathered by the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System, which quantifies rates of opioid abuse in the United States, tapentadol IR was associated with a low population-based rate of abuse and diversion. In that study,[14] rates of tapentadol IR abuse during the 24 months after its approval were comparable to those of tramadol and lower than abuse rates associated with hydrocodone and oxycodone. In a separate retrospective cohort study evaluating the risk of opioid doctor shopping for tapentadol IR compared with oxycodone IR,[15] the risk of opioid shopping behavior for patients exposed to oxycodone IR was 3.5 times greater than that for patients exposed to tapentadol IR.

Tapentadol extended release (ER; NUCYNTA® ER, Janssen Pharmaceuticals, Inc.) received US FDA approval in August 2011 for the management of moderate to severe, chronic pain in adults and in August 2012 for the management of neuropathic pain associated with diabetic peripheral neuropathy in adults; for both indications, tapentadol ER is intended for use when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Tapentadol ER tablets are formulated with a polyethylene oxide (PEO) matrix using a melt extrusion manufacturing process to produce hardened tablets of high mechanical strength that are resistant to crushing and extraction (INTAC® tamper-resistant technology, Grünenthal, Aachen, Germany).[16] In keeping with the recommendations of different governmental agencies that abuse-deterrent opioid formulations should be developed to hinder typical methods of oral opioid abuse,[9-11] PEO-based tapentadol tablets are expected to have tamper-resistant properties. These properties were evaluated using a battery of analytical and physical characterization tests. This article reports the results of mechanical attempts to alter the physical structure and release properties of these PEO-based tablets.

METHODS

The resistance of tapentadol ER tablets to simulated tampering was evaluated using different assays. Simulations of potential forms of accidental misuse/recreational abuse-first level (including methods that might be used by patients and/or healthcare providers to facilitate swallowing) included the following: attempting to crush tablets between two spoons; attempting to crush tablets using a professional pill crusher; application of forces up to 1,000 N (two- to

four-times greater than the mean human chewing force of 220-475 N[17]) using a standardized pharmacopeia breaking force tester; attempting to dissolve intact (untampered) tablets and tablets subjected to the pill crusher in a standard quality control (QC) medium; and attempting to dissolve intact tablets in a 40 percent ethanol solution. To simulate recreational abuse-second level, attempts were made to crush the tablets using a standardized hammer instrument, to crush frozen tablets using the standardized pharmacopeia breaking force tester, to dissolve intact tablets and tablets subjected to hammering in standard QC medium, and to extract the active ingredient from intact tablets and tablets subjected to hammering in a range of readily available solvents (eg, 5 percent ethanol, 0.1 N HCl, water). For all analytical and physical characterization tests performed, one or more of the following dose strengths of tapentadol ER were used: 50, 100, 150, 200, and 250 mg. Experimental details for these simulations are summarized below.

Crush resistance

To evaluate the mechanical resistance of tapentadol ER tablets to crushing, an attempt to crush each dose strength (50, 100, 150, 200, and 250 mg) was made using the following four tools and methods: two commercially available metal spoons applied in a grinding motion; a professional metal pill crusher (Ocelco Inc.) closed once; a standardized pharmacopeia breaking force tester (Current USP <1217>), which exerted forces of up to 1,000 N during a single application; and a standardized hammer instrument, which dropped a 5-kg steel weight once from a height of 80 cm onto the tablet (equal to an impact energy of 39.2 Nm). The use of the standardized hammer instrument was considered to be a more rigorous and controlled test than a manual strike with a regular hammer.

The standardized pharmacopeia breaking force tester was also used to evaluate the crush resistance of frozen tablets of each dose strength. Tapentadol ER tablets were frozen in bulk at –20°C, removed from the freezer, and tested immediately. As with the nonfrozen tablets, the breaking force tester was used to apply forces of up to 1,000 N to the frozen tablets.

All crushing tests were performed in triplicate. After each attempt to crush a tapentadol ER tablet, the tablet was visually inspected. For the tablets subjected to tampering using spoons or the professional pill crusher, the dimensions of the tablets were measured before and after tampering. The mean length, width, and height were calculated for each dose strength of tapentadol ER tablets before and after tampering. The 250-mg tapentadol ER tablet has the lowest ratio of PEO to active ingredient and therefore should be the most susceptible to attempts at tampering. For that reason, only results for crush resistance testing of the 250-mg tablets are presented here.

Dissolution characteristics

To evaluate in vitro drug-release profiles, dissolution in 900 mL of standard QC medium (0.050 M phosphate buffer, pH 6.8) was performed for intact tapentadol ER tablets (50 and 250 mg) and tablets subjected to tampering with the professional pill crusher and the standardized hammer instrument. For dissolution experiments, only the lowest (50 mg) and highest (250 mg) dose strengths were evaluated because these two doses represented the extremes of the PEO to active ingredient ratio within the dose range evaluated; the 50-mg tablet has the highest PEO to active ingredient ratio, and, as previously mentioned, the 250-mg tablet has the lowest PEO to active ingredient ratio.

Testing was performed using a USP Apparatus 2 (Paddle) at 100 rpm. A sinker was used to prevent the tablets from sticking to the surfaces of the vessel containing a standard solvent. The quantity of tapentadol present in the dissolution samples was determined using ultraviolet (UV) spectrophotometry at a detection wavelength of 272 nm.

To evaluate the effects of alcohol on dissolution of intact tapentadol ER tablets, the same QC dissolution method was used, but the dissolution medium was replaced with a 40 percent ethanol/60 percent USP buffer (pH 6.8). All dissolution tests were performed in triplicate.

Resistance to extraction in liquids

The resistance to extraction in liquids of intact 250-mg tapentadol ER tablets and tablets subjected to tampering with the hammer instrument was evaluated in 10 different solvents: isopropanol, acetone, ethyl acetate, 40 percent ethanol, absolute ethanol, methanol, water, 0.1 N HCl, 0.1 N NaOH, and organic food corn oil.

Intact and hammered 250-mg tapentadol ER tablets were shaken intensely using a mechanical shaker (model Gerhardt Laboshake) in 30 mL of each respective solvent, and the solutions were sampled after 15 minutes and after 1 hour of nonstop shaking. The amount of tapentadol extracted was determined using reversed-phase high-performance liquid chromatography with UV detection (273 nm). Separations were performed on a YMC-Pack ProC18 RS column (100 mm × 3.0 mm i.d., 3 µm particle size; YMC America, Inc.) using a gradient of 10 mM phosphate buffer (pH 7.5), acetonitrile, and methanol. The flow rate was 0.5 mL/min and the column temperature was 35°C. All extractions were performed in triplicate. The mean amount of active ingredient extracted in each solvent was calculated.

RESULTS

Crush resistance

For all dose strengths, no deformation of tapentadol ER tablets was observed when two metal spoons were used in an attempt to crush the tablets. A 250-mg tablet subjected to tampering with spoons is shown in Figure 1. The dimensions of the intact and tampered tablets for the three attempts to crush the 250-mg tablet using two spoons are shown in Table 1. The differences in the mean length, width, and height of the 250-mg tablet before and after tampering with spoons were all 0 mm.

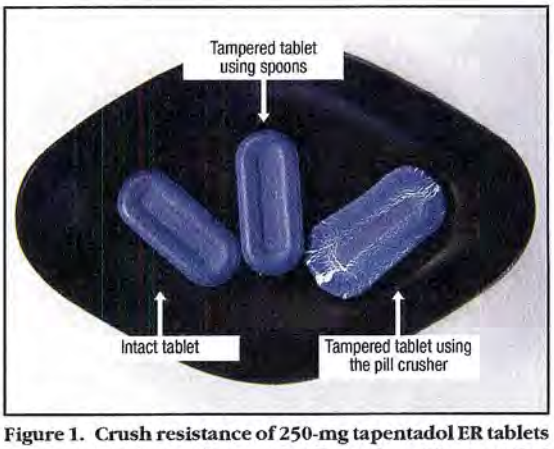

Figure 1. Crush resistance of 250-mg tapentadol ER tablets to spoons and a professional pill crusher. ER, extended release.

When the professional pill crusher was used in an attempt to crush tapentadol ER tablets, minimal deformation, with no pulverization or breakage, was observed for all dose strengths. A 250-mg tablet subjected to tampering with the pill crusher is shown in

Table 1. Dimensions of 250-mg tapentadol ER tablets before and after tampering with 2 spoons or a professional pill crusher*

Tablet	Dimensions of intact tablets, mm			Dimensions of tampered tablets, mm		
	Length	Width	Height	Length	Width	Height
Two spoons						
1	20.0	9.1	4.3	20.0	9.1	4.3
2	20.4	9.1	4.3	20.3	9.1	4.3
3	20.2	9.1	4.4	20.2	9.1	4.4
Mean	20.2	9.1	4.3	20.2	9.1	4.3
Professional pill crusher						
1	20.3	9.1	4.3	21.7	11.3	3.5
2	20.3	9.1	4.3	22.8	12.3	3.2
3	20.3	9.1	4.4	21.9	11.3	3.5
Mean	20.3	9.1	4.3	22.1	11.6	3.4

ER, extended release.
*Crushing tests were performed in triplicate.

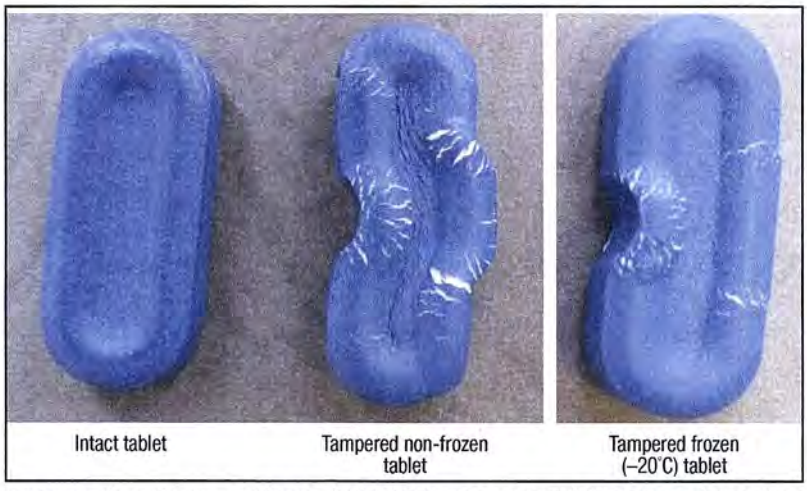

Figure 2. Crush resistance of nonfrozen and frozen (–20°C) 250-mg tapentadol ER tablets subjected to tampering using a breaking force tester. ER, extended release.

Figure 1. The dimensions of the intact and tampered tablets for the three attempts to crush the 250-mg tablet using a professional pill crusher are shown in Table 1. Differences in the mean dimensions of the 250-mg tablet were +1.8 mm for the length, +2.5 mm for the width, and –0.9 mm for the height.

When the standardized pharmacopeia breaking force tester (at 1,000 N) was used, tapentadol ER tablets of all dose strengths were slightly deformed, but not crushed or broken (breaking force >1,000 N). When tapentadol ER tablets were frozen at –20°C and subjected to the standardized pharmacopoeia breaking force tester (at 1,000 N), results were similar to those observed with nonfrozen tablets. None of the tablets were crushed or broken; the tablets were slightly deformed. Nonfrozen and frozen 250-mg tablets tested using the breaking force tester are shown in Figure 2.

For the simulation of recreational abuse-second level using the standardized hammer instrument, all tapentadol ER tablets were completely flattened, but not pulverized or broken into pieces. A 250-mg tablet subjected to tampering by hammering is shown in Figure 3.

Crush resistance results comparable to those for the 250-mg tablet were obtained for the other four dose strengths when subjected to tampering efforts using two spoons, a professional pill crusher, a standardized pharmacopoeia breaking force tester, and a standardized hammer instrument (data not shown).

Dissolution characteristics

For tapentadol ER tablets of the low- and high-dose levels (50 and 250 mg) subjected to tampering with a professional pill crusher, the mean in vitro release profile in a standard QC medium was similar to intact tablets. The mean in vitro release profiles of intact 50- and 250-mg tablets and tablets subjected to tampering using a professional pill crusher are shown in Figure 4.

For 50- and 250-mg tapentadol ER tablets subjected to tampering with the standardized hammer instrument, the in vitro release profile in a standard QC medium was somewhat faster than for intact tablets; the percentage of active ingredient released after 30 minutes was approximately 15-19 percent for intact tablets and 30 percent for hammered tablets. This

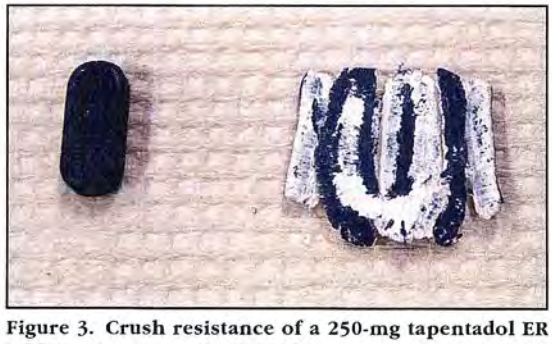

Figure 3. Crush resistance of a 250-mg tapentadol ER tablet using a standardized hammer instrument. ER, extended release.

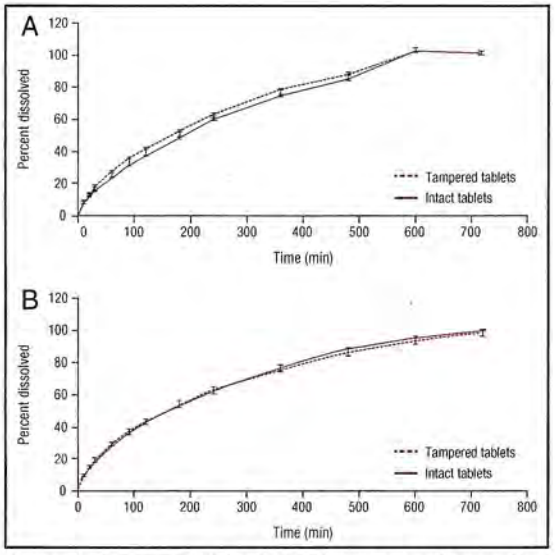

Figure 4. Mean ± SD (the SD is shown at each sampling time point) in vitro release profiles in the QC medium of A) 50-mg and B) 250-mg tapentadol ER tablets subjected to tampering with a professional pill crusher. SD, standard deviation; ER, extended release; and QC, quality control.

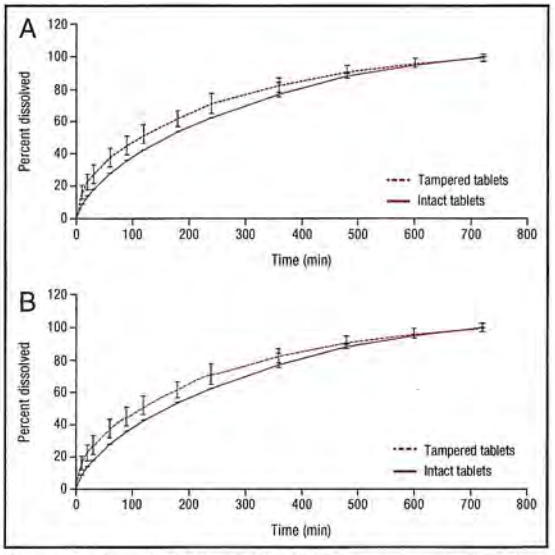

Figure 5. Mean ± SD (the SD is shown at each sampling time point) in vitro release profiles in the QC medium of A) 50-mg and B) 250-mg tapentadol ER tablets subjected to tampering with a standardized hammer instrument. SD, standard deviation; ER, extended release; and QC, quality control.

percentage of release is only slightly higher than the maximum release allowed per drug product specifications (25 percent in 30 minutes) for untampered, marketed tablets. The mean in vitro release profile of 50- and 250-mg tablets subjected to tampering using the hammer instrument is shown in Figure 5.

In the 40 percent ethanol solution (representative of a concentrated alcohol beverage), the in vitro release profiles for intact tapentadol ER 50- and 250-mg tablets were slower than in the QC medium, indicating no dose dumping in either medium. The mean in vitro release profiles for 50- and 250-mg tapentadol ER tablets in a 40 percent ethanol solution and in the QC medium are shown in Figure 6.

Resistance to extraction in liquids

Intact tapentadol ER tablets were resistant to extraction in five of the organic solvents tested (acetone, absolute ethanol, ethyl acetate, isopropanol, and organic food corn oil) after 15 minutes and after 1 hour of shaking (Figure 7A). The mean amount of drug extracted with acetone was 0 percent after 15 minutes and 0.2 percent after 1 hour; in absolute ethanol, the mean amount extracted was 0.1 and 0.4 percent, respectively. Intact tapentadol ER tablets were completely resistant to extraction

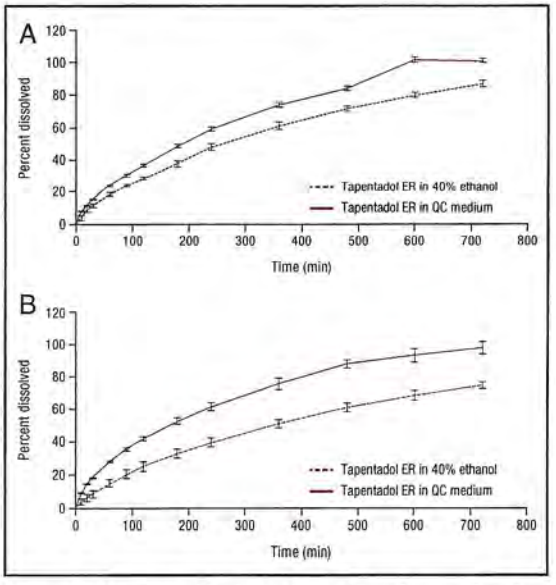

Figure 6. Mean ± SD (the SD is shown at each sampling time point) in vitro release profiles of intact A) 50-mg and B) 250-mg tapentadol ER tablets dissolved in the QC medium and in a 40 percent ethanol solution. SD, standard deviation; ER, extended release; and QC, quality control.

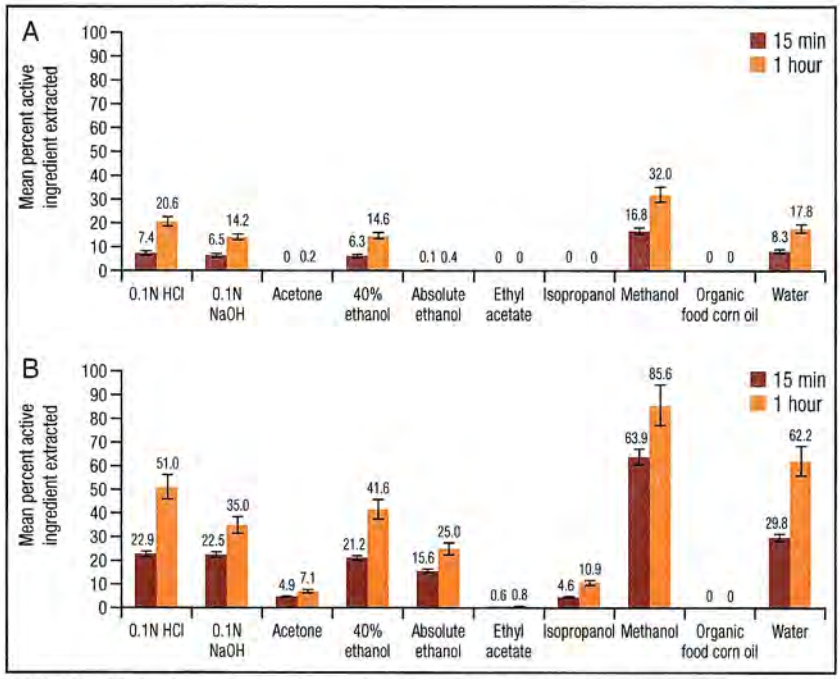

Figure 7. Mean ± SD (the SD is shown for each sample) amounts of active ingredient extracted (% label claim) in different solvents for A) intact 250-mg tapentadol ER tablets and B) hammered 250-mg tapentadol ER tablets. SD, standard deviation and ER, extended release.

with shaking in ethyl acetate, isopropanol, and organic food corn oil. In aqueous solvents (0.1 N HCl, 0.1 N NaOH, 40 percent ethanol, and water), the amount of drug extracted with shaking from the intact tablets increased with the extraction time. The mean amount of drug extracted in these solvents ranged from 6.3 to 8.3 percent at 15 minutes and from 14.2 to 20.6 percent at 1 hour (Figure 7A). The amount of drug extracted in methanol with shaking also increased with the extraction time. The mean amount extracted was 16.8 percent at 15 minutes and 32.0 percent at 1 hour (Figure 7A).

For tapentadol ER tablets that had been subjected to tampering with a standardized hammer instrument, the mean amount of drug extracted with shaking in acetone, ethyl acetate, isopropanol, and organic food corn oil ranged from 0 to 4.9 percent at 15 minutes and from 0 to 10.9 percent at 1 hour (Figure 7B). Although the amount of drug extracted with shaking increased with the extraction time in 0.1 N NaOH, 40 percent ethanol, and absolute ethanol, the mean amount extracted at 1 hour was less than 50 percent for all three solvents and ranged from 15.6 to 22.5 percent at 15 minutes and from 25.0 to 41.6 percent at 1 hour (Figure 7B). The amount of drug extracted with shaking also increased with extraction time in 0.1 N HCl, water, and methanol, and more than 50 percent of the drug was extracted at 1 hour in these three solvents; the mean amounts extracted were 22.9, 29.8, and 63.9 percent, respectively, at 15 minutes and 51.0, 62.2, and 85.6 percent, respectively, at 1 hour (Figure 7B).

DISCUSSION

This study evaluated the resistance of tapentadol ER tablets formulated with a PEO matrix to accidental misuse/recreational abuse-first level and recreational abuse-second level. According to the findings presented here, the PEO matrix provided resistance to crushing of these tablets using spoons, a professional pill crusher, or a standardized pharmacopeia breaking force tester. Using a standardized hammer instrument, the tablets were flattened, but not pulverized or broken into pieces. These results indicate that this formulation is mechanically resistant to tampering via accidental misuse and contains properties that may deter tampering by recreational abusers.

For tablets subjected to tampering with a professional pill crusher, which is the most severe crushing technique used by healthcare professionals or patients, no change was observed in the extended-release profile compared with intact tablets, based on dissolution testing in a standard QC medium. The extended-release profile was also largely unaffected for hammered tapentadol ER tablets. These results indicate that this formulation prevents immediate release of the active ingredient, even when subjected to the harshest crushing method that might be used by a healthcare professional or patient or to a tampering method more likely to be used by a recreational abuser (ie, hammering). An evaluation of the potential effect of combining intact tapentadol ER tablets with a concentrated alcoholic beverage yielded similar results. The in vitro drug-release profile for intact tapentadol ER tablets in a medium with high alcohol content was slower than in the QC medium, indicating no dose dumping in either medium.

In extraction tests in different readily available media, intact tapentadol ER tablets were resistant to dissolution in five solvents (acetone, ethyl acetate, isopropanol, absolute ethanol, and organic food corn oil). The mean amount of drug extracted from intact tablets in aqueous solvents (0.1 N HCl, 0.1 N NaOH, 40 percent ethanol, and water) and in methanol increased with time but remained at or below 32 percent at 1 hour for all solvents. Tablets subjected to hammering were still largely resistant to extraction in acetone, ethyl acetate, isopropanol, and corn oil (amount extracted, ≤10.9 percent at 1 hour). In aqueous solvents, the mean amount of drug extracted from hammered tablets was up to approximately 62 percent at 1 hour, while the mean amounts of drug extracted in methanol and ethanol were approximately 85 and 25 percent, respectively. Solvents that partially dissolved intact tapentadol ER tablets (methanol, 0.1 N HCl, 0.1 N NaOH, 40 percent ethanol, and water) would require additional steps to remove the solvents and obtain the active ingredient. In addition, the toxicity of methanol could potentially serve as a deterrent for abusers considering using this solvent for dissolution of tapentadol ER. Although tablets subjected to hammering were less resistant to extraction than intact tablets, release of more than 50 percent of the active ingredient occurred in only three of the 10 tested solvents with vigorous shaking over extended periods of time.

The ease with which tapentadol ER formulated with the PEO matrix could be converted into desirable forms for abuse by experienced opioid abusers was evaluated in a recent pair of studies.[18] Less than 25 percent of experienced abusers were willing to snort tapentadol ER particles, and less than 4 percent of the active ingredient was extracted from tapentadol ER tablets (vs 37 percent with a nontamper-resistant oxycodone ER formulation).[18] The time required to tamper with tapentadol ER tablets was also significantly longer than the time required to tamper with oxycodone ER tablets ($p \leq 0.05$).[18] The physical properties observed in the present study, which would deter abuse and misuse, may underlie the difficulty that experienced abusers had in tampering with tapentadol ER tablets.[18]

CONCLUSIONS

Pain is the most common complaint for patients seeking the help of a medical professional.[19] A recent Internet-based survey yielded a weighted point prevalence for moderate to severe, chronic pain of approximately 25 percent in a US population.[20] Many patients with severe, chronic noncancer pain experience inadequate pain management.[21] The World Health Organization (WHO) and other advocacy groups have sought to promote the belief that adequate pain management is a fundamental human right.[22] One factor that may relate to this issue of inadequate pain management and that may contribute to physicians' underuse of opioids in patients who might benefit from opioid therapy is the potential for abuse. To overcome the barriers that limit the delivery of effective chronic pain treatment, physicians must establish a treatment plan that uses universal precautions to reduce the risk of abuse, misuse, and diversion.[23] The use of tamper-resistant formulations may allow physicians to help mitigate patients' concerns about subjective discrimination related to patient selection for treatment with tamper-resistant opioids. Based on proposed legislation in the United States, tamper-resistant formulations may soon become the standard[10]; until such time, tamper-resistant formulations should at least be considered as part of an opioid abuse-deterrent strategy. Therefore, by routinely prescribing tamper-resistant opioid formulations for all the patients who require opioid medication, potential selectivity bias or discrimination toward those patients and their pain management may be reduced. The impact of tamper-resistant technologies on abuse, addiction, misuse, and diversion is

not known; nonetheless, these technologies are aligned with current US public health, regulatory, legislative, and medical licensing boards' efforts to create opioid abuse-deterrent strategies that are not expected to limit access to opioid therapy for appropriate patients. In April 2013, the FDA approved a change to the label for OxyContin® (oxycodone HCl controlled release; Purdue Pharma, LP, Stamford, CT) describing the tamper-resistant properties of the new formulation that should deter abuse by injection or the intranasal route.[24] In addition, the FDA concluded that the abuse potential associated with the original OxyContin® formulation was sufficient to refuse approval of any new generic drug applications that were contingent on the approval of the original formulation.[24] There is no fail-proof precautionary measure to completely deter prescription opioid abuse. Nevertheless, the development of tamper-resistant formulations, which may address some of the concerns about opioid abuse that previously hindered use in patients who require opioid analgesics for their pain management, represents an important first step in the management of pain as a disease, rather than as a symptom.

Although no drug can be completely tamper-proof, results of this battery of analytical and physical tests indicate that tapentadol ER formulated with a PEO matrix has properties that impede tampering, particularly tampering with the intent of achieving rapid release of the active ingredient from the tablet. Along with the results of previous studies showing the low abuse potential for tapentadol relative to other opioids[14,25] and low desirability of tapentadol ER for experienced opioid abusers,[18] results of the present study of the tamper-resistant properties of tapentadol ER suggest that tapentadol ER is likely to be associated with a relatively low risk of abuse and misuse, which may further facilitate appropriate management of chronic pain.

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